IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Pascale Pouzet *et al.* Examiner: Rebecca L. Anderson

Serial No.: 10/058,456 Group Art Unit: 1626

Filed: January 28, 2002 Docket: 1/1168

For: ALKYLPHENYLIMINOIMIDAZOLIDINE DERIVATIVES FOR TREATING URINARY INCONTINENCE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HISATO KITAGAWA UNDER 37 C.F.R. § 1.132

I, Hisato Kitagawa, declare that:

1. In 1986, I was awarded a Doctorate/Ph.D. from the University of Kyoto, Faculty of Medicine, Japan.

2. Since 1974, I have worked for Nippon Boehringer Ingelheim, where I am currently responsible for Pharmacology and where I am currently a project leader of Drug Discovery.

3. I am a coinventor of the above-identified patent application (hereinafter "the Pouzet *et al.* application") and I am familiar with the Pouzet *et al.* application.

4. Under my responsibility and control, compounds according the Pouzet *et al.* application were investigated to determine the metabolic rate and bioavailability with the purpose of using these compounds in the treatment of urinary incontinence. The following test protocols were used for determining the metabolic rate:

   Test A: A 30 microM formulation of the respective compound was incubated with the enzyme rat liver microsome and the degradation of the respective compound after 60 minutes was determined.

   Test B: Under the same test conditions as for Test A, the enzyme human liver microsome was used instead of the enzyme rat liver microsome.

   The following test protocol was used for determining the bioavailability:

Test C: The test substances were administered orally to a group of eight (8) male fasted rats. As a control, animals in an identical second group were given the test substances intravenously. At specified times after administration (10 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours, and additionally 6 hours in the case of the animals in the oral group) 1 mL blood samples were taken from the animals in both groups. The blood samples taken in each group were mixed together (8 mL). The content of the corresponding test substances in the blood for the appropriate time was determined from the plasma after further working up by high performance liquid chromatography (HPLC) using standard methods and correlated for the two groups.

5. In the Tests A and B of the above paragraph 4, compound 5'-chloro-3'-isopropyl-2'-methylphen-1'-yl-2-iminoimidazolidine (Example 27 of the Pouzet *et al.* application) showed a metabolic rate of 0.42 for rat liver microsome and 0.15 for human liver microsome. 3'-*tert*-Butyl-6'-methoxyphen-1'-yl-2-iminoimidazolidine (Example 2 of the Pouzet *et al.* application) showed a metabolic rate of 0.47 for rat liver microsome and 0.08 for human liver microsome.

6. In the Test C of the above paragraph 4, 5'-chloro-3'-isopropyl-2'-methylphen-1'-yl-2-iminoimidazolidine (Example 27 of the Pouzet *et al.* application) showed a bioavailability of 24%. 3'-*tert*-Butyl-6'-methoxyphen-1'-yl-2-iminoimidazolidine (Example 2 of the Pouzet *et al.* application) showed bioavailability of 34%.

7. To compare the compounds of the Pouzet *et al.* application with compounds according to the Esser *et al.* application (WO 96/32939) the same Tests A, B, and C of above paragraph 4 were conducted for 2-(6'-bromo-3'-dimethylamino-2'-methylphenylimino)imidazolidine (Example 2 of the Esser *et al.* application). In Test C, 2-(6'-bromo-3'-dimethylamino-2'-methylphenylimino)imidazolidine showed a bioavailability of 0.7%.

7. From the above comparative experiments and the results, I conclude that for the treatment of urinary incontinence, 5'-chloro-3'-isopropyl-2'-methylphen-1'-yl-2-iminoimidazolidine and 3'-*tert*-butyl-6'-methoxyphen-1'-yl-2-iminoimidazolidine of the Pouzet *et al.* application possess unexpectedly superior metabolic stability and higher

bioavailability in comparison to 2-(6'-bromo-3'-dimethylamino-2'-methylphenylimino)imidazolidine of the Esser *et al.* application.

8. Furthermore, I conclude that this superiority was unexpected in view of the cited prior art. Moreover, I conclude that such superiority would have been both surprising and unexpected to one of ordinary skill in the art of the subject matter of the invention.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: July 23, 2003 Signature: _____
Hisato Kitagawa